

# Developmental origins of environmental reproductive health and fertility compromise

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There is growing evidence that stem cells are important components of numerous, if not all, tumors. Thus, investigating the contribution of spermatogonial stem cells to testicular cancer is an obviously important area of study, and may contribute to our understanding of the “testicular dysgenesis syndrome” (TSD) presented by Drs. Skakkebaek and Sharpe. However, it is also possible that environmental disruption of the spermatogonial stem cell niche could lead to decreases in sperm counts, without inducing the complete TSD in men. The spermatogonial stem cell niche fills a pocket defined by a basement membrane and the extended arms of Sertoli cells, surrounding undifferentiated spermatogonia that are maintained in their resident state of self-renewal and the potential to differentiate into clonal spermatogonia and eventual evolution into mature sperm. Thus, disruption of the stem cell niche, whether during development or in the adult, will have an adverse effect on sperm output and ultimately on total sperm counts.

Regulation of the stem cell population requires a balance between maintenance, differentiation, and self-renewal. Current literature has demonstrated that signals for this regulation are extrinsic, primarily from the Sertoli cell but also from the interstitium, as well as intrinsic factors found within the stem cells. These factors may differ during development and adulthood, as our recent report found that deletion of the transcription factor *ets*-related molecule (ERM; also known as *ets* variant 5) resulted in a first wave of spermatogenesis but a failure of stem cell self-renewal and thus loss of subsequent germ cells (1). An examination of control human testicular tissues often reveals focal areas of hypospermatogenesis and even missing early generations of spermatogonia, suggestive of a similar failure of spermatogonial self-renewal. Based upon the fact that testes recovery from irradiation takes years in humans, and recovery of spermatogenesis can be

very slow or absent in rodents following some toxic exposures, it is possible that the remaining stem cells fail to self-renew or do not fill the stem cell niches in a timely manner. A better understanding of this process and the mechanisms involved is essential as we try to link experimental reproductive toxicity and human reproductive dysfunction.

Finally, another goal of this meeting was to explore new directions. In the experimental arena, the new technique of spermatogonial stem cell transplant appears to offer tremendous opportunities for more rapid extrapolation of potential toxic effects of chemicals on human spermatogenesis. Direct transplant of germ cells from larger species into rodent testes provides a unique way to test more economically the effects on primate tissues (2). Digesting the testicular components first and manipulating gene expression in different cell types before transplanting the mixture under the back skin of the nude mouse permits the testis to rebuild *in vivo* (3, 4). This technique will allow for more rapid discovery of molecular mechanisms because of endocrine disruption of human spermatogenesis.

## REFERENCES

1. Hess RA, Cooke PS, Hofmann MC, Murphy KM. Mechanistic insights into the regulation of spermatogonial stem cell niche. *Cell Cycle* 2006;5:1164–70.
2. Brinster RL, Avarbock MR. Germline transmission of donor haplotype following spermatogonial stem cells. *Proc Natl Acad Sci USA* 1994;91:11303–7.
3. Schlatt S, Honaramooz A, Ehmcke J, Goebell PJ, Rübber H, Dhir R, et al. Limited survival of adult human testicular tissue as ectopic xenograft. *Hum Reprod* 2006;21:384–9.
4. Honaramooz A, Magee SO, Rathi R, Dobrinski I. Building a testis: formation of functional testis tissue after transplantation of isolated porcine (*Sus scrofa*) testis cells. *Biol Reprod* 2007;76:43–7.

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